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(FILE 'HOME' ENTERED AT 12:40:12 ON 18 MAY 2004)

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SEA HEPARANASE

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FILE 'DGENE, BIOSIS, CAPLUS, SCISEARCH, MEDLINE, EMBASE, USPATFULL, TOXCENTER, CANCERLIT, BIOTECHNO, ESBIODASE' ENTERED AT 12:41:38 ON 18 MAY

L1

2004

L2 174 S L1 AND (SPLICE VARIANT OR HEPARANASE-2)  
L3 123 S L2 AND (ISOLAT? OR PURIF?)  
L4 123 DUP REM L3 (0 DUPLICATES REMOVED)

FILE 'BIOSIS, CAPLUS, SCISEARCH, MEDLINE, EMBASE, USPATFULL, TOXCENTER,  
CANCERLIT, BIOTECHNO, ESBIODBASE' ENTERED AT 12:47:29 ON 18 MAY 2004

L5 313 S L1 AND (VARIANT OR MUTANT OR SPLICE VARIANT)  
L6 225 S L5 AND (PURIF? OR ISOLAT?)  
L7 1 S L6 AND (HEPARANASE-2)  
L8 187 DUP REM L6 (38 DUPLICATES REMOVED)  
L9 104 S L1 AND (SPLICE VARIANT)  
L10 104 DUP REM L9 (0 DUPLICATES REMOVED)

L8 ANSWER 180 OF 187 CANCERLIT on STN

ACCESSION NUMBER: 93696451 CANCERLIT

DOCUMENT NUMBER: 93696451

TITLE: The molecular cloning and characterization of human **heparanase** cDNA and the immunochemical localization of **heparanase** in metastatic melanomas.

AUTHOR: Jin L

CORPORATE SOURCE: Univ. of Texas H.S.C. at Houston Grad. Sch. of Biomed. Sci.

SOURCE: Diss Abstr Int [B], (1993) 53 (11) 5515.

ISSN: 0419-4217.

DOCUMENT TYPE: (THESIS)

LANGUAGE: English

FILE SEGMENT: Institute for Cell and Developmental Biology

ENTRY MONTH: 199311

ENTRY DATE: Entered STN: 19941107

Last Updated on STN: 19970509

AB **Heparanase**, an endo-beta-D-glucuronidase, has been associated with melanoma metastasis. Polyclonal antibodies directed against the murine N-terminal **heparanase** peptide detected a Mr of approx 97,000 protein upon SDS-polyacrylamide gel electrophoresis of mouse melanoma and human melanoma cell lysates. In an indirect immunocytochemical study, metastatic human A375-SM and mouse B16-BL6 melanoma cells were stained with the antiheparanase antibodies. **Heparanase** antigen was localized in the cytoplasm of permeabilized melanoma cells as well as at the cell surface of unpermeabilized cells. Immunohistochemical staining of frozen sections from syngeneic mouse organs containing micrometastases of B16-BL6 melanoma demonstrated **heparanase** localized in metastatic melanoma cells, but not in adjacent normal tissues. Similar studies using frozen sections of malignant melanomas resected from patients indicated that **heparanase** is localized in invading melanoma cells, but not in adjacent connective tissues. Monoclonal antibodies directed against murine **heparanase** were developed and characterized. Monoclonal antibody 10E5, an IgM, precipitated and inhibited the enzymatic activity of **heparanase**. A 2.6-kb cDNA was isolated from a human melanoma lambda gt11 cDNA library using the monoclonal antibody 10E5. Heparan sulfate cleavage activity was detected in the lysogen lysates from E coli Y1089 infected with the lambda gt11 cDNA and this activity was inhibited in the presence of 10-fold excess of heparin, a potent inhibitor of **heparanase**. The nucleotide sequence of the cDNA was determined and insignificant homology was found with the gene sequences currently known. The cDNA hybridized to a 3.2-3.4 kb mRNA in human A375 melanoma, WI-38 fibroblast, and THP-1 leukemia cells using Northern blots. **Heparanase** expression was examined using Western and Northern blots. In comparison to human A375-P melanoma cells, the quantity of 97,000 protein recognized by the polyclonal anti-**heparanase** antibodies doubled in the metastatic **variant** A375-SM cells and the quantity of 3.2-3.4 kb mRNA doubled in A375MetMix, a metastatic **variant** similar to A375-SM cells. In B16 murine melanoma cell, the intensity of the 97,000 protein increased more than 2 times comparing with B16-F1 cells. The extent in the increase of the protein and the mRNA levels is comparable to the change of **heparanase** activity observed in those cells. In summary, the studies suggest that (a) the N-terminus of the **heparanase** molecule in mouse and human is antigenically related; (b) **heparanase** antigens are localized at the cell surface and in the cytoplasm of metastatic human and mouse melanoma cells; (c) **heparanase** antigens are localized in invasive and metastatic murine and human melanomas in vivo, but not in adjacent normal tissues; (d) **heparanase** molecule appeared to be differentially expressed at the transcriptional as well as at the translational level; and (e) the size of human **heparanase** mRNA is 3.2-3.4 kb. (Full text available from University Microfilms International, Ann Arbor, MI, as Order Number AAD93-07237)

ACCESSION NUMBER: 1985:362764 BIOSIS  
DOCUMENT NUMBER: PREV198580032756; BA80:32756  
TITLE: SEQUENTIAL DEGRADATION OF HEPARAN SULFATE IN THE  
SUBENDOTHELIAL EXTRACELLULAR MATRIX BY HIGHLY METASTATIC  
LYMPHOMA CELLS.  
AUTHOR(S): BAR-NER M [Reprint author]; KRAMER M D; SCHIRRMACHER V;  
ISHAI-MICHAELI R; FUKS Z; VLODAVSKY I  
CORPORATE SOURCE: DEP RADIATION AND CLIN ONCOL, HADASSAH UNIV HOSP, PO BOX  
12000, JERUSALEM 91 120, ISRAEL  
SOURCE: International Journal of Cancer, (1985) Vol. 35, No. 4, pp.  
483-492.  
CODEN: IJCNAW. ISSN: 0020-7136.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB A highly metastatic **variant** (ESb) of a methylcholanthrene-induced T lymphoma elaborates a heparan sulfate (HS) degrading endoglycosidase (**heparanase**) to a much higher extent than its non-metastatic parental subline (Eb). Whereas a serum-free medium conditioned by either subline contained a trypsin-like serine protease, **heparanase** activity was detected only in the ESb-conditioned medium (CM). ESb CM was incubated with a naturally produced, sulfate-labeled subendothelial extracellular matrix (ECM) or with a soluble, high-MW labeled proteoglycan first released from the ECM by incubation with Eb CM or with the partially **purified** ESb protease. Sulfate labeled degradation products were analyzed by gel filtration on Sepharose 6B. The optimal pH for degradation of ECM-bound HS was 6.2 as compared to pH 5.2 for degradation of the soluble proteoglycan. **Heparanase**-mediated degradation of both ECM-bound and soluble HS was inhibited by heparin. Addition of either trypsin, plasmin or to a lower extent, the **purified** ESb protease, stimulated between 5- and 20-fold the ESb CM-mediated degradation of ECM-bound HS but had no effect on **heparanase**-mediated degradation of the soluble proteoglycan. This stimulation was inhibited in the presence of heparin or protease inhibitors. These results indicate that both a protease and heparinase are involved in the ESb-mediated degradation of ECM-bound HS and that 1 enzyme produces a more accessible substrate for the next enzyme. This sequential cleavage is characteristic of degradation of a multimolecular structure such as the subendothelial ECM and hence cannot be detected in studies with its **isolated** constituents.

L8 ANSWER 181 OF 187 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
DUPLICATE 7

ACCESSION NUMBER: 1994:20409 BIOSIS  
DOCUMENT NUMBER: PREV199497033409  
TITLE: Nerve growth factor effects on human and mouse melanoma  
cell invasion and **heparanase** production.  
AUTHOR(S): Marchetti, Dario [Reprint author]; Menter, Dave; Jin, Li;  
Nakajima, Motowo; Nicolson, Garth L.  
CORPORATE SOURCE: Dep. Tumor Biol., Box 108, Univ. Texas M.D. Andersen Cancer  
Cent., 1515 Holcombe Blvd., Box 108, Houston, TX 77030, USA  
SOURCE: International Journal of Cancer, (1993) Vol. 55, No. 4, pp.  
692-699.  
CODEN: IJCNAW. ISSN: 0020-7136.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 25 Jan 1994  
Last Updated on STN: 26 Jan 1994

AB The role of growth factor networks in regulating the progression of human  
melanocytes towards tumorigenicity and ultimately the malignant phenotype  
is poorly understood. In particular, the autocrine and paracrine  
influences that modulate cellular invasion and extracellular matrix  
degradative enzymes of melanoma cells remain undefined at the molecular  
level. We report here that nerve growth factor (NGF) can modify some  
metastasis-associated cellular properties of human and mouse melanoma  
cells. Treatment of early-passage human metastatic melanoma cells (MeWo)  
or their **variants** (3S5, 70W) with biologically active 2.5S NGF  
resulted in (a) delayed density-dependent inhibition of melanoma cell  
growth; (b) increased in vitro invasion through a reconstituted basement  
membrane; and (c) time- and dose-dependent induction of **heparanase**  
, a heparan-sulfate-specific endo-beta-D-glucuronidase associated with  
human melanoma metastasis. These effects of NGF were most marked in the  
70W brain-colonizing cells (70W gt MeWo gt 3S5). The NGF enhancement of  
**heparanase** secretion was not species-specific, since it was also  
observed in murine B16 melanoma cells; the highest NGF stimulation of  
**heparanase** was found in brain-colonizing murine B16-B15b  
**variant** (B 16-B15Sb gt B16BL6, B16-F10, B16-F1). NGF also  
increased the invasive capacity of the human 70W and murine B16-B15b  
sublines in a chemoinvasion assay performed with filters coated with  
**purified** heparan sulfate proteoglycan (HSPG). The enhancement of  
chemotactic response and **heparanase** production was detected at  
NGF concentrations sufficient to fully saturate both low- and  
high-affinity NGF receptors (NGFR), the neurotrophin receptor (p75) and  
the trkA gene product, respectively. The results suggest that, in  
addition to the effects of NGF on cellular development and differentiation  
within the peripheral and central nervous systems, NGF can exert changes  
in the invasive properties of neuroectoderm-derived melanoma cells.

L10 ANSWER 104 OF 104 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:472900 CAPLUS

DOCUMENT NUMBER: 135:73335

TITLE: A human **heparanase** sequence homolog and  
**splice variants** and their possible  
therapeutic use in the control of invasive cell  
proliferation

INVENTOR(S): Mckenzie, Edward Alexander; Stamps, Alasdair Craig;  
Terrett, Jonathan Alexander; Tyson, Kerry Louise

PATENT ASSIGNEE(S): Oxford Glycosciences (Uk) Ltd., UK

SOURCE: PCT Int. Appl., 97 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001046392	A2	20010628	WO 2000-GB4963	20001221
WO 2001046392	A3	20011206		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1240313	A2	20020918	EP 2000-985677	20001221
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2003517835	T2	20030603	JP 2001-546890	20001221
US 2003083254	A1	20030501	US 2002-177245	20020621
PRIORITY APPLN. INFO.:			GB 1999-30392	A 19991222
			GB 2000-8713	A 20000407
			WO 2000-GB4963	W 20001221

AB A human sequence homolog of **heparanase** and a number of variants  
that can arise from alternative splicing are described. The protein may  
play a role in the control of heparan-dependent invasive cell growth in a  
number of pathologies and may therefore be a target for therapeutics.  
Identification of an EST for a **heparanase** homolog in a com.  
sequence database, PCR cloning of a cDNA and anal. of tissue distribution  
of the mRNA are reported.

L10 ANSWER 99 OF 104 USPATFULL on STN  
 ACCESSION NUMBER: 2002:126341 USPATFULL  
 TITLE: **Heparanase** II, a novel human  
**heparanase** paralog  
 INVENTOR(S): Heinrikson, Robert Leroy, Plainwell, MI, UNITED STATES  
 Bienkowski, Michael Jerome, Portage, MI, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002064853	A1	20020530
APPLICATION INFO.:	US 2001-836461	A1	20010417 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-199072P	20000420 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Edward F. Rehberg, Pharmacia & Upjohn Company, Global Intellectual Property, 301 Henrietta Street, Kalamazoo, MI, 19001	
NUMBER OF CLAIMS:	46	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	4 Drawing Page(s)	
LINE COUNT:	2288	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a cDNA encoding a heretofore unknown enzyme termed **heparanase** II; constructs and recombinant host cells incorporating the cDNA; the **heparanase** II polypeptide encoded by the gene; antibodies to the polypeptide; and methods of making and using all of the foregoing.